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**Conization for preinvasive and early invasive carcinoma
of the uterine cervix**

By Göran Larsson



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**Conization
for preinvasive and early invasive carcinoma
of the uterine cervix**

Göran Larsson

From the Department of Obstetrics and Gynecology,
University of Lund, Lund, Sweden

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ORIGINAL PAPERS

This thesis is based on the following publications, which will be referred to in the text by their Roman numerals:

- I. Larsson, G.: Conization for cervical dysplasia and carcinoma in situ: Long term follow-up of 1013 women. *Ann Chir Gynaecol* 70:79, 1981.
- II. Larsson, G., Grundsell, H., Gullberg, B. & Svennerud, S.: Outcome of pregnancy after conization. *Acta Obstet Gynecol Scand* 61:461, 1982.
- III. Larsson, G., Alm, P. & Grundsell, H.: Laser conization versus cold knife conization. *Surg Gynecol Obstet* 154:59, 1982.
- IV. Larsson, G., Gullberg, B. & Grundsell, H.: A comparison of complications of laser and cold knife conization. *Obstet Gynecol*. In press.
- V. Grundsell, H., Alm, P. & Larsson, G.: Cure rates after laser conization for early cervical neoplasia. *Ann Chir Gynaecol*. In press.
- VI. Larsson, G., Alm, P., Gullberg, B. & Grundsell, H.: Prognostic factors in early invasive carcinoma of the uterine cervix. A clinical, histo-pathological and statistical analysis of 343 cases. *Am J Obstet Gynecol*. In press.

ABBREVIATIONS

AC

after conization

BC

before conization

CIS

carcinoma in situ

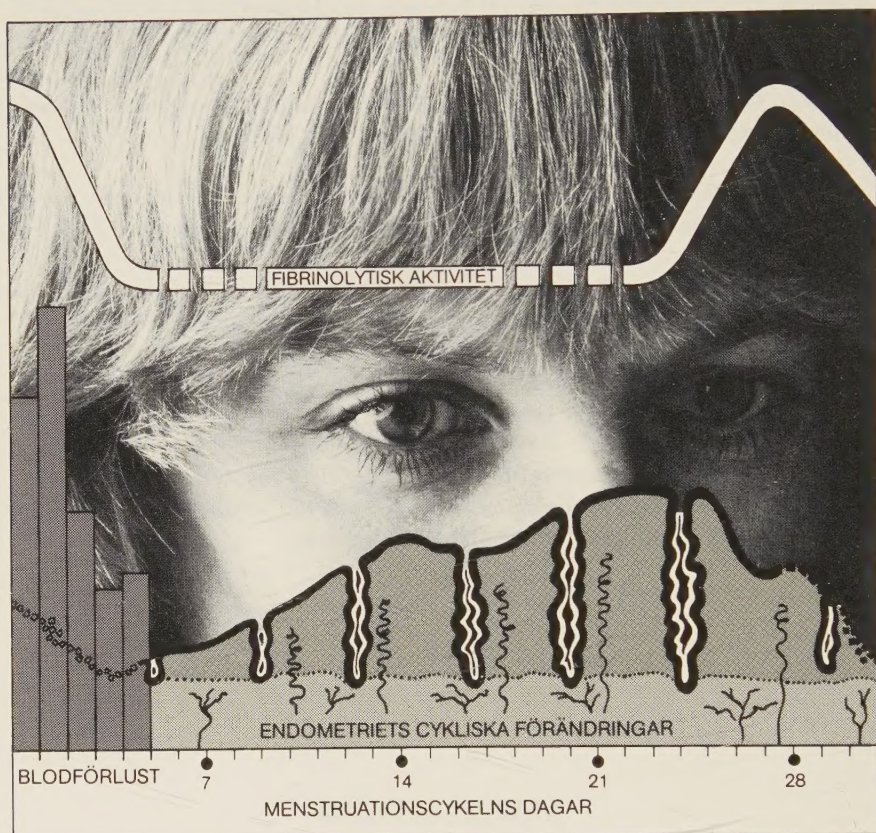
CL-invasion

invasion of tumor cells or tumor thrombi in capillary-like endothelial-lined spaces in cases of early invasive carcinoma of the uterine cervix

RR

relative risk

Kvinnor med menorrhagi har en förhöjd fibrinolytisk aktivitet i endometriet*



Antifibrinolytisk behandling med Cyklokapron

- ges bara under menstruationsperioden • reducerar blodförlusten med 50%
- har effekt redan första behandlingsdagen • är icke hormonell
- kan anpassas av patienten beträffande dos och duration

* Rybo G. Plasminogen activators in the endometrium. Acta Obstet Gynecol Scand 45 (1966) p 429.

Cyklokapron[®]
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SHARPLAN KIRURGILASER

OPERERAR MED CO₂-teknik.

SHARPLAN kirurgilaser arbetar inom ett strikt avgränsat operationsområde. Det ger ett minimum av vävnadsskador och blödningar.

Principen för laseroperationer är att tillsluta blodkärl.

Genom minskade vävnadsskador och en begränsning av blödningar efter operationen, påvisas en klar minskning av antalet vård dagar för patienter opererade med laser.

För optimal precision vid laseroperationer rekommenderas WILD operationsmikroskop.

Kontakta oss för konsultation och demonstration av SHARPLAN kirurgilaser.

Vi lämnar också förslag på referensanläggningar samt tillhandahåller litteratur om kirurgilaser.

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HISTORICAL BACKGROUND AND INTRODUCTION

THE CONIZATION OPERATION AND ITS PREDECESSORS

Operations on the uterine cervix in women were probably first performed by Ambroise Paré in the 16th century and about a century later by Tulipus of Amsterdam in 1652 (240). These operations were high amputations. In the first half of the 19th century amputations were performed by Duputren, Récamier and Hugier in cases presumed to be carcinoma of the uterine cervix. Later investigations, however, demonstrated that these cases were not cancer but chronic inflammation with induration and hypertrophy of the cervix.

Lisfranc, in 1815, also in cases presumed to be early cancer, removed a wedge-shaped block extending from the vaginal margin of the cervix up to the internal os (245). The wound surface was allowed to heal by secondary intention, which took 5 to 6 weeks. This is probably the first time the open conization technique was described. Stenosis and strictures of the cervical canal were frequent after Lisfranc's operation.

The method was revised by Sims, who in 1861 described that the wound surface could be covered with healthy vaginal mucosa "much in the same manner that a stump of an arm or leg is covered after amputation by the circular method" (351). This was done by passing four sutures of silver wire through the anterior and posterior borders of the wound which, when tightly drawn, brought its edges into apposition in a straight line across the middle of the stump, covering it completely, but leaving a small opening just over the outlet of the cervical canal. The silver sutures were removed in a week.

The latter part of the 19th century was characterized by an extensive literature, describing different operative techniques used on the uterine cervix, mainly for chronic cervicitis and lacerations, but in some instances also for invasive cervical carcinoma. Well-known gynecologists such as Hegar, Simon, Marckwald, Pouey, Pozzi, Jayle and Simpson have all described operative modifications (240). Before long, however, two methods gained prominence over all others: Emmet's trachelorrhaphy in USA and England and Schröder's operation in Europe.

It was on September 28, 1874 that Thomas Addis Emmet read his famous paper before the Medical Society of the County of New York (116). The operation consisted of excision of cervical lacerations and primary coaptation of the surfaces with interrupted silver sutures.

Carl Schröder devised in 1878 conization-like operations for invasive cervical carcinoma and for chronic cervicitis (340). He operated upon cervical carcinoma stage IIA and less by conically extirpating the cervix together with an ample vaginal cuff and claimed that his operation was superior to Freund's abdominal operation for invasive cervical carcinoma (135). For chronic cervicitis his operation consisted of conical extirpation of the cervical mucosa and parts of the stroma from the anterior and posterior lips separately. The wound was primarily sutured.

From 1890 there appeared a number of articles and monographs reporting the postoperative results and also the outcome of pregnancy after the described operations. The results of these investigations were summarized by Leonard, who also made investigations of his own of postoperative cure and outcome of pregnancy after amputation and trachelorrhaphy (240, 241). His conclusions were that amputation of the uterine cervix should be avoided in childbearing years; that trachelorrhaphy had no deleterious effect on subsequent pregnancies but on the other hand often proved to be ineffective to cure the chronic infection if the cases were not highly selected.

Called upon by this, Sturmdorf in 1916 devised a technique which would permit removal of all the diseased mucosa and which later would show not to complicate further pregnancies to the same extent as amputation (363). After mobilisation of the vaginal mucosa, he excised a cone from the cervix and covered the wound with his wellknown stitch. After recognition of preinvasive carcinoma of the uterine cervix it was this operation that was, and some places still is, used for diagnostic and therapeutic purposes. The Sturmdorf operation quickly became very popular and it was generally agreed that it cured chronic cervicitis in a high percentage of cases. It was also claimed to have no or little influence upon subsequent pregnancies (71, 263, 311, 373).

In 1928 the so called electroconization was introduced for the first time by Hyams (184). The tissue was excised with a string through which passed electric current. The method was further developed by Crossen (98), Champion (82) and by Miller & Todd (276) and became very popular on the European continent (39, 111, 171, 227, 275, 317). It is hardly used any more because the coagulated resection margins are difficult to evaluate at histo-pathological investigation.

Modern cold conization technique has benefitted from the so called bloodless technique of Scott, in which vasoconstrictors (usually epinephrine or vasopressin) are injected submucosally and into the stroma (62, 63, 102, 345). The practice to leave the cone cavity open to heal by secondary intention began gradually in the 50s (302). The aim was to achieve better cosmetic results than with the Sturmdorf method, which, however, still survives as the most popular method for closing cervical stroma and achieving primary healing. Lateral sutures, Sturmdorf sutures, suture according to Coppersmith-Reid (91), vaginal packing, electrocoagulation of the wound surface, heat coagulation according to Semm (104), colposcopically guided conizations due to reduction of cone size (72, 399) and special knives (156, 193, 293, 348, 356) are all claimed to reduce the frequency of postoperative hemorrhages. The few studies where different techniques have been used fail to verify this (89). Controlled studies are not available. Cold knife conization has remained an operation associated with high morbidity (37, 50, 55, 75, 83, 89, 100, 107, 168, 173, 190, 216, 297, 334, 357, 401, 415).

THE DISEASE (PREINVASIVE AND EARLY INVASIVE CARCINOMA OF THE UTERINE CERVIX) AND ITS DETECTION

Carcinoma in situ of the uterine cervix was first described by J. Williams in a Harveian Lecture in 1886 (402). He stated: "This is the earliest condition of undoubted cancer of the portio vaginalis which I have met with, and it is the earliest condition which is recognizable as cancer. It is superficial and remains superficial for a long time." Later Cullen in 1900 (99), Schauenstein in 1908 (331) and Schottländer & Kermanner in 1912 (338) described squamous carcinoma in situ in the periphery of invasive carcinoma. Rubin, in 1910, described two cases of carcinoma in situ not associated with invasive carcinoma and concluded

that this was cervical cancer in its preclinical form (324).

In the middle 20s two diagnostic tools became available: colposcopy through Hinselmann (170), later further developed by Antoine & Grünberger (11), and the iodine staining test of Schiller (335).

However, carcinoma in situ remained a rare diagnosis until Papanicolaou published his work on cell studies on the uterine cervix in 1941 (304). This was in the middle of World War II. The full importance of Papanicolaou's work was not recognized until the early 50s in the USA and late 50s in Europe. The increased detection rate of carcinoma in situ started a debate as to the nature of the lesion. There was a great reluctance on the part of many pathologists to make the diagnosis of malignancy in the absence of invasion. This prompted gynecologists to perform retrospective as well as prospective studies.

By 1949 Galvin & Te Linde in a retrospective study presented 17 cases of their own and from others, where carcinoma in situ had progressed to invasive carcinoma (142). Stoddard, in 1952, accepted 42 cases (359). Prospective studies by Karlstedt (197), Petersen (310) and Younge (410) clearly demonstrated the invasive potential of carcinoma in situ.

The relationship between various degrees of dysplasia, carcinoma in situ and invasive carcinoma is beyond the scope of this thesis and will not be discussed further. It should only be mentioned that the prevailing attitude is that they form a continuum (320). This had led to the introduction of the CIN-nomenclature (cervical intraepithelial neoplasia) (318, 319) where CIN I corresponds to mild dysplasia, CIN II to moderate dysplasia and CIN III to severe dysplasia and carcinoma in situ.

With the increased use of the Papanicolaou smear test, leading to more frequent use of diagnostic biopsies and conizations, apart from preinvasive changes, also very early invasive carcinomas were detected. Mestwerdt, in 1947, coined the expression Mikrokarcinom for these early invasive lesions (273). Since then about 20 different names have been given to the entity (252). No generally accepted definition exists as to what constitutes early invasive carcinoma of the uterine cervix. Mestwerdt (273) allowed 5 mm penetration from the basement membrane into the stroma. Others allow 1 mm (109), 3–4 mm (382), 5 mm (136, 260, 279) or even 9 mm (382), the 5 and 3 mm definitions being most frequently used. Only one official metric definition exists, namely the one of the Society of Gynecologic Oncologists in the USA (46).

This society defines early invasive carcinoma as tumors which have penetrated 3 mm or less into the stroma from the base of the epithelium. FIGO (International Federation of Gynecologists and Obstetricians), in the 1974 classification, gives no metric definition. Sometimes a subdivision into very early cases and into somewhat more advanced ones is recommended (66, 253).

Tumor extension in three directions (tumor volume) has also been used to define early invasive carcinoma (67, 238, 295). Some authors exclude cases with confluent growth and tumor invasion in capillary-like spaces (CL-invasion) from the category of early invasive carcinoma (87, 105, 260, 289, 371, 382). This discrepancy in definitions has made comparison between different treatment modalities difficult.

THE LASER

The term laser is an abbreviation for light amplification by stimulated emission of radiation. The laser theory was first proposed in 1958 by Schawlow & Townes (332). The laser action may be obtained from solids, liquids and gases. By supplying these media with energy their atoms or molecules are stimulated to higher energy levels, leading to emission of photons or electromagnetic radiation, characterized by parallelism, monochromacy and coherency, thus the properties of laser light.

The first laser, the ruby laser, was developed in 1960 by Maiman. It was a solid laser, where laser action was obtained from a ruby crystal by supplying it with intense flashes of light. Each flash of energy created laser radiation at a wavelength of 0.69 microns. Corresponding to the flashes the laser beam was produced in pulses or bursts of a very short duration, usually a fraction of a millisecond. Experimental use of the ruby laser in tumor surgery showed that the heavy impact of this pulsed laser could cause the spread of viable tumor cells into the stroma and into the blood vessels and lymphatics (203). It was therefore soon abandoned.

The neodymium-YAG laser, also a solid laser, was developed in 1961 by Johnson and Nassau, and has found its use mainly in urology and gastro-enterology. The argon laser, a gas laser, is used above all among ophthalmologists.

The CO₂ laser, the predominant laser in gynecology, was developed by Patel in 1964 (306). It is a molecular gas laser. Clinical application began in

1972. Pioneers in clinical gynecologic work with the CO₂ laser were J.H. Bellina, New Orleans, USA (29), R. Toaff, Tel Aviv, Israel, (372) and the man who has done most to introduce the CO₂ laser into clinical surgery, professor Isaac Kaplan, Tel Aviv, Israel (195).

The effects of the CO₂ laser on tissues *in vivo* have been summarized by Hall (160). He could demonstrate that the tissue is incised by the boiling of intra- and extracellular water, which forms steam that disrupts the tissue and that the temperature of laser impact is 100 degrees Celsius, implying that all DNA is destroyed. It could also be demonstrated that the zones of thermal necrosis and thermal damage adjacent to the incision were only about 50–100 microns and 500 microns respectively and that the CO₂ laser had the ability to seal vessels with a diameter up to 0.5 mm.

TRENDS IN THE TREATMENT OF PREINVASIVE AND EARLY INVASIVE CARCINOMA OF THE UTERINE CERVIX

There are marked differences in the treatment of preinvasive and early invasive carcinoma of the uterine cervix between different countries.

Preinvasive carcinoma

USA. When Galvin and Te Linde in 1949 recommended a modified radical Wertheim hysterectomy with removal of 2 cm parametrium on each side together with a wide vaginal cuff but omitting lymph gland dissection and leaving one ovary in young women as treatment for CIS, they were criticized for their conservatism (121, 142, 266, 308, 333). Their article, however, started a debate as to the optimum treatment of CIS, which is still going on, and which has resulted in innumerable publications. Graham and Meigs stated in 1952 that it was not necessary to extirpate the parametrium and that ended the debate on that issue (148). From this year on simple hysterectomy (abdominal or vaginal) with or without vaginal cuff became the most common form of treatment in the USA (23, 25, 48, 79, 94, 103, 120, 124, 140, 146, 157, 161, 183, 206, 230, 231, 264, 278, 279, 282, 283, 288, 307, 334, 341, 368, 381, 390, 393, 406).

Some of these authors state that they, under very special circumstances in young women with a strong desire for further childbirth, who fully understand the nature of the disease and who accept regular and close check-ups, are willing to let conization be the only treatment.

A somewhat more liberal attitude towards conization as treatment is represented by Peightal (309), Carter (80), Parker (305), Adelman (3), Ayre (18) and Younge (411).

The first to propose that a cone with margins free from atypic cells was treatment enough for CIS irrespective of age and desire for further childbirth were Enterline and Krieger & McCormack (118, 219, 220, 221, 222).

Their proposal prompted several investigators to study the frequency of persistent disease in hysterectomy specimens after conization (23, 48, 103, 126, 144, 146, 159, 161, 181, 258, 264, 278, 307, 309, 334, 341, 344, 350, 370, 393, 405). Reported figures vary between 10 and 70%. However, the importance of the margins of the cone (involved or not involved) was seldom recognized in these studies.

Apart from certain centres, where cryosurgery (43, 85, 96, 97, 187, 199, 375, 376, 383, 387) and laser vaporization (2, 21, 22, 29, 30, 70, 81, 262) have been used, simple extrafascial hysterectomy has remained the treatment of choice in the USA (47, 137, 290, 369, 391).

The "in between therapy" of conization as treatment for the majority of cases is practised in only a few places (149, 190, 329, 357).

Canada. British Columbia, in 1949, was the first place in the world to start cytologic mass screening of its female population. A cone with CIS but margins free from atypic cells has been recommended as sufficient therapy for fertile women (51, 78, 130) and later irrespective of age (53). In practice, however, 75% of women with CIS reported from British Columbia have been treated with simple hysterectomy. Recently tissue destructive methods have been introduced (31, 243, 312, 388, 407).

New Zealand and Australia. These two countries early developed a conservative attitude towards the treatment of CIS. Green, New Zealand, concluded that conization was sufficient treatment and that most cases with cone margins not free from atypic cells were free from disease at follow-up (150, 152). In the 60s conization was the treatment of choice in Australia (91, 92, 265, 353). Electrocoagulation diathermy has become the tissue destructive method of choice in Australia (83, 84).

England. In the 60s and 70s only a minority advocated conization with free margins as only treatment

for CIS (38, 134, 242, 267, 268, 269). The standard treatment was hysterectomy (7, 8, 58, 412) or even modified radical hysterectomy with a vaginal cuff, as strongly advocated by Way (395) and officially supported by a leading article in *Lancet* (229).

In the late 70s conization became more popular (205) as well as tissue destructive methods, advocated above all by Singer and Jordan (191, 352) and Anderson (10).

European continent. Already from the beginning in the early 50s conization was recognized and also practised as treatment enough for CIS (13, 14, 40, 44, 55, 61, 65, 73, 74, 77, 143, 145, 147, 154, 169, 172, 178, 198, 200, 201, 207, 209, 223, 224, 228, 248, 256, 272, 280, 281, 286, 292, 297, 299, 300, 301, 303, 316, 327, 342, 347, 379, 385, 386, 404, 413). Also the fact that the majority of patients with cones with non-free margins had negative cytology at follow-up was early observed (20, 76, 127, 169, 171, 177, 179, 180, 217, 218, 297, 362, 384, 415).

Only a minority of authors have recommended hysterectomy or extended hysterectomy as treatment (1, 19, 56, 112, 246, 247, 259, 291, 336, 337).

Tissue destructive methods have been used very seldom (166) and based on investigations of the relationship between prognosis and diagnostic material, where the best prognosis was achieved when the diagnosis was based on a conization specimen (68), strong warnings against tissue destructive treatment have been given (69).

Scandinavia. The Scandinavian countries excluded the hysterectomy stage to a great extent and started early to perform conization as both diagnosis and treatment for CIS, of which many cases were detected in the mass screening programs, which started early (4, 41, 114, 122, 141, 167, 196, 204, 211, 213, 214, 215, 216, 225, 226, 325, 355, 364).

Materials where a larger proportion of patients have been treated with hysterectomy are rare (208, 249, 354, 366, 416).

Around 1973 a debate started as to whether conization was over-treatment for CIS (255). Thereafter local excision, electrocoagulation and cryosurgery have been used in selected cases at certain centres (5, 113, 115, 164, 165, 188, 378).

Early invasive carcinoma

Mestwerdt, who first called attention to the treatment of very early invasive carcinomas of the uterine

cervix, recommended that a cone with margins free from atypic cells be treatment enough in young women with a desire for further childbirth (274). Before Mestwerdt, also very early invasive cases had been treated with radical surgery or full irradiation treatment. His statement initiated a vivid discussion as to the optimum treatment of these early cancers.

The majority of authors have recommended simple hysterectomy (abdominal or vaginal; with or without vaginal cuff) and sometimes conization as treatment for what they define as stage IA cervical carcinoma (17, 49, 52, 59, 64, 66, 67, 86, 87, 88, 90, 95, 96, 105,

110, 119, 123, 125, 129, 131, 133, 136, 138, 162, 163, 175, 185, 186, 198, 232, 233, 238, 251, 253, 260, 278, 279, 284, 287, 295, 298, 313, 314, 322, 323, 328, 330, 339, 346, 349, 365, 367, 380, 392, 400, 409, 412).

Extended hysterectomy has been practised by Zinser (414), Way (394), Kolstad (212), Beecham (26), Yajima (408) and di Re (106).

Some authors claim that also early invasive carcinoma should be treated with radical Wertheim hysterectomy and bilateral pelvic lymphadenectomy (12, 15, 16, 34, 45, 55, 101, 139, 192, 234, 244, 250, 271, 326, 342, 343, 360, 389).

AIMS OF THE PRESENT INVESTIGATION

1. To analyse in a large number of cold knife conizations early and late complications and cure rates (I and II).
2. To develop a new operative procedure associated with less morbidity than cold knife conization (III and IV).
3. To evaluate the effectiveness of this new procedure at least during a short follow-up time (V).
4. To evaluate the role of conization in the treatment of early invasive carcinoma of the uterine cervix (VI).

PATIENT MATERIAL

1013 women underwent cold knife conization during the 17-year period from January 1, 1962 to December 31, 1978. No woman was pregnant at the time of conization. The largest age group was 25–29 years and mean age was 34 years. Conization was the only primary treatment in patients with smears positive or suspicious of squamous cell malignancy. If, in smears with lesser degrees of atypicality, four quadrant biopsy or endocervical curettage revealed CIS or severe dysplasia, conization was also performed. Follow-up after conization consisted of a vaginal smear and a gynecologic examination after three months and six months, then every sixth month for five years, and thereafter once a year. All women have been followed for at least one year and the majority of them for more than five years. The longest period of follow-up was 17 years. Colposcopy was not routinely used (I).

988 of the 1013 women had their conization performed during 1962–1976. 197 of these 988 became pregnant AC with a total of 635 pregnancies BC and AC. 37 of the 197 women had not been pregnant BC. The outcome of the pregnancies was studied as well as the effect of prophylactic cerclage. Term delivery was defined as gestational age >36 weeks, premature delivery as ≤ 36 weeks, late spontaneous and legal abortion as >12 weeks, early spontaneous and legal abortion as gestational age ≤ 12 weeks. Comparable age groups within the material BC and AC were analysed, considering, apart from age, increasing parity, socio-economic status, smoking habits, surgical interventions and various diseases. The classification of socio-economic status was based on the occupation of the woman and/or her husband (II).

110 consecutive women underwent conization of the cervix uteri because of vaginal smears indicating severe dysplasia or CIS during the period June to December 1980. Colposcopy was performed preoperatively in all cases. All of the women were prospectively randomized into one of two groups. No woman was pregnant at the time of conization. In one group, conization was performed with a carbon dioxide laser, equipped with a flexible arm for free hand excisional surgery. In the other group of women, conization was performed with the cold knife technique. Early hemorrhage was defined as bleeding postopera-

tively requiring some type of intervention and occurring within the first four days after operation. Late hemorrhage was defined as the same kind of bleeding occurring after the fourth postoperative day (III).

884 women had three different types of conization performed: 428 were hospitalized for cold knife conization (group 1). 216 were hospitalized for laser conization (group 2) and 240 underwent laser conization as an out-patient procedure (group 3). None was pregnant at the time of conization. All conizations were performed between June 1, 1979 and July 1, 1982. Laser conization was introduced in May 1980 and has gradually replaced cold knife conization. During 1979 151 conizations were performed, all belonging to group 1. During 1980 140 operations belonging to group 1 and 68 belonging to group 2 were performed. During 1981 110, 132 and 111 conizations of groups 1, 2 and 3 respectively were performed. For 1982 the corresponding figures were 27, 16 and 129. The hospitalized patients arrived at the department the morning before operation and left as a rule on the second postoperative day. The average stay was 4 days. The out-patients arrived half an hour before operation and left after 3–4 hours. Mean ages for the three groups were 34.6, 33.8 and 35.0 years and ranges were 19 to 63 years, 20 to 60 years and 19 to 67 years respectively. Mean parity before conization was 1.76, 1.79 and 1.54. Mean number of spontaneous and legal abortions were 0.43, 0.36 and 0.36. Mean number of extrauterine pregnancies were 0.03, 0.02 and 0.00. Mean gravity was 2.22, 2.17 and 1.90. In the different groups 32.7%, 37.0% and 38.9% of patients were on oral contraceptives. Insertion of intrauterine device at conization was undertaken in 23.9%, 25.5% and 21.7% respectively. Of the conizations 5.4%, 6.0% and 5.4% were reconizations. The first consecutive 109 patients in group 2 were given a questionnaire in which they were to note for how long they experienced bleeding, discharge and pain and were requested to return it (IV).

333 non-pregnant women, who underwent laser conization between May 1980 and January 1982 because of abnormal vaginal smears suggesting severe dysplasia or CIS, were followed with cytology and colposcopy for 4 to 24 months after operation. Col-

poscopy was performed in all patients before operation, but usually no biopsies were taken. Both exocervical and endocervical lesions were included. 134 of the patients (40.2%) underwent conization as an outpatient procedure. Mean age was 34.1 years and range was 19 to 62 years. Mean parity and gravity were 1.6 and 2.0 respectively. After the operation the patients were regularly checked by vaginal cytologic smear examination and colposcopy after 4–6 months and thereafter every 6th month. With respect to the histo-pathological findings of the cone specimens, patients with changes of early invasive carcinoma or resection margins not free from atypic cells were checked more frequently (V).

343 patients with a histo-pathological diagnosis of early invasive cervical carcinoma made during the 20-year period 1960–1979 and with a uterine cervix free from clinical suspicion of malignancy were analysed for factors of prognostic importance and for the possible role of conization as treatment for this early tumor. No *a priori* definition of early invasive carcinoma was adopted. The material available for study consisted of 46 cases of removed uteri, 160 cases of adequate conizations, where the whole tumor focus or foci were removed *in toto*, and in 58 cases a combination of these types. Another 79 cases, where the diagnosis was based on several large wedge biopsies with normal endocervical curettings, were included in

order to compare the adequacy of this diagnostic material vis-à-vis the conization and hysterectomy specimens.

The clinical part of the investigation concerned the 264 patients, for whom the diagnosis was based on conization, uterus or both. Mean and median age for these patients were 42.5 and 41 years respectively and range was 23 to 85 years. The following histo-pathological variables were studied: tumor depth, lateral extension of tumor, type of infiltration, histologic type, degree of differentiation, invasion or strong suspicion of invasion in lympho-vascular spaces (CL-invasion) and borders of a diagnostic cone. The depth of penetration into the underneath stroma was measured perpendicular from the basement membrane at the site of origin of invasion (surface epithelium or endocervical cleft) with the aid of a calibrated ocular micrometer. The lateral extension of the tumor was also measured (*i.e.* in a direction along the surface epithelium and perpendicular to the stroma infiltration). When there were multiple foci of invasion, the tumor lateral extension was the sum of the lateral extensions of all foci.

Clinical variables studied were: age, symptoms and gynecologic examination at the time of diagnosis, cytology reports, type of treatment and subsequent fate of the patients (VI).

OPERATIVE PROCEDURES

CONIZATION

All conizations were done under general anesthesia. The patients who had a cold knife conization were hospitalized. Laser conizations were performed both on hospitalized patients and as an out-patient procedure. To reduce bleeding, the descending branches of the uterine arteries were tied with No. 0 chromic catgut (I and II) and with a No. 0 dexone suture (III, IV and V) and adrenalin solution (1 ml 0.1% adrenalin in 100 ml saline; to 382 patients presented in I and II) or vasopressin (Postacton^R, Ferring, Sweden, 20 IU/ml, 0.5 ml in 60 ml saline; to the rest of the patients presented in I and II and to the patients in III, IV and V) was injected into the cervix. During the operation 1 g of the fibrinolytic inhibitor tranexamic acid (Cyklokapron^R, Kabi, Sweden) was given as an intravenous infusion (III – V) and after the operation 1 g was given orally three times a day for two weeks to all patients after introduction of Cyklokapron in Sweden.

The base of the cone was determined with the aid of Schiller's test and on patients in III-V it was also guided by the colposcopic extension of the lesion. The length of the cervix was measured with a uterine sound. In studies I and II a Hegar dilator was introduced through the internal os and the top of the cone was adjusted to be just distal to the internal os and not engaging it. In studies III, IV and V no Hegar dilator was used and in cases of only exocervical changes not all the cervical canal up to the vicinity of the internal os was extirpated.

The cone specimen was extirpated with a cold knife or with a carbon dioxide laser. The laser was a Sharp-lan 733 (Laser Industries, Tel Aviv, Israel) equipped with a flexible arm for free hand surgery. Laser action was created in an optical cavity, where a mixture of 4.5% CO₂, 13.5% N₂ and 82% of He was excited by high-energy electrical discharges and produced the invisible laser light, which was reflected in a system of mirrors in the flexible arm onto the focusing lens and further into the tissue. A helium-neon laser of 2 mW power output with a visible red aiming beam operated coincident with the CO₂ laser beam and provided a

visual target at the treatment site. The focal length of the lens was 125 mm and the spot size (beam diameter on target with the laser in a focused position) was 0.22 mm. The laser conizations were performed with 25 – 30 W of power output, resulting in power densities of 68 000 to 80 000 W per square centimeter. The mode of action was continuous.

A circular incision corresponding to the base of the cone was first made with the laser. A pair of Allis' forceps was applied to the edge of the cone avoiding the exocervical resection margins, and with a slight traction on the forceps while deepening the incision with the laser, the cone was delivered. After extirpation of the cone with the laser, the cone cavity was superficially fulgurated with the beam in a defocused position at 20 W power output. When laser operations were performed, the patient and all personnel in the operating room wore protective glasses. Direct contact between the eye and the laser beam may result in damage of the cornea. Signs on the doors to the operating room indicated that laser surgery was going on.

A curettage was always performed after removal of the cone specimen and the resultant cavity was left open to heal by secondary intention. All patients were recommended to rest for two weeks and to avoid intercourse and baths for four weeks.

CERCLAGE OPERATION

Women in study II, who became pregnant after conization during the period 1970 to 1976, had a prophylactic cerclage applied in gestational week 13–14. The operation was performed under general anesthesia. A nylon band (Braun Melsungen AG), with one needle at each end, was introduced in the posterior fornix and drawn submucosally on each side of the cervix to the anterior fornix, where the needles were allowed to penetrate the mucosa and the two ends of the band were tied. The cerclage was removed at the onset of labor.

HISTO – PATHOLOGICAL CONSIDERATIONS

All cones were marked with a suture at twelve o'clock for orientation. In I and II the cones were put into 10% formaldehyde solution for fixation and sent to the laboratory. In III, IV and V they were sent to the laboratory in a fresh state and on arrival there they were cut open, stretched and attached longitudinally to a cork plate and thereafter fixed in 10% formaldehyde solution. Twentyfive to fifty thin slices were then cut sagittally and further processed for paraffin embedding. For histo-pathologic evaluation in light microscopy, sections, cut at a thickness of 6 micrometers, were stained in hematoxylin and eosin.

All margins of resection, *i.e.* exocervical, deep and apical, were judged with regard to whether or not the pathological changes had been totally excised. Free margins of resection (resection margins free from cells with atypias) implied only normal epithelium at all cut edges. Not even slight dysplasia was allowed. Doubtfully free margins of resection meant that it was not possible with certainty to decide whether all margins of resection contained only normal squamous or columnar epithelium. If changes ranging from mild dysplasia to invasive carcinoma occurred at one or more margins of the cone, the resection margins were judged as not free.

The diagnostic criteria of mild, moderate, severe dysplasia and CIS remained uniform throughout the different studies. In mild dysplasia the pathologic cells occupied the lower third of the epithelium, in moderate dysplasia the lower two-thirds, in severe dysplasia almost all the epithelium and in CIS all the epithelium (296).

The CIN (cervical intraepithelial neoplasia) nomenclature (319) has been used in IV and V. CIN I corresponds to mild dysplasia, CIN II to moderate dysplasia and CIN III to severe dysplasia and carcinoma in situ.

In I microinvasive carcinoma was defined according to Mestwerdt's original definition (273) as penetration of tumor cells 5 mm or less beyond the basement membrane. In IV and V the 3 mm limit was used. In VI no *a priori* definition of early invasive carcinoma was adopted. Furthermore, in this study six different types of infiltration were recognized: area infiltration, fingerlike infiltration, invasive buds, confluent growth, combinations and adenocarcinomas. The definition of area infiltration was in accordance with that of Przybora (314). Invasive buds could be clearly differentiated from CIS with extension into endocervical clefts.

The following histologic types of early invasive carcinoma were recognized: large cell keratinizing tumors, large cell non keratinizing tumors, small cell tumors and adenocarcinomas. The degree of differentiation was high, moderate or poor. In cases of very early infiltration it was not possible to determine histologic type and degree of differentiation. Tumor thrombi or tumor cells in endothelial-lined capillary-like spaces was defined as CL-invasion. Strong suspicion of CL-invasion implied tumor cells growing on the outer side of the endothelial-lined capillary-like spaces, but with no actual invasion seen, despite additional sections.

CYTOLOGY

The cytologic smears consisted of samples from the endocervix, the portio and the posterior fornix in all patients. The smears indicating conization in studies I and II were evaluated at the Cytologic Laboratory, Malmö General Hospital, Malmö, Sweden. They were classified as follows (361): Group I — normal cells; Group II — cellular atypia, probably benign and of inflammatory origin; Group III — moderate to severe atypia with cells showing signs of malignant changes in the nucleus but with well-differentiated cytoplasm (dyskaryotic cells); Group IV — suspicion of squamous cell carcinoma with mainly dyskaryotic

cells but also one or more cells with a reversed nucleus/cytoplasm ratio; Group V — diagnostic of squamous cell carcinoma with clearly malignant cells having an irregular nuclear structure and reversed nucleus/cytoplasm ratio.

The vaginal smears indicating conization in studies III–V were analysed at the Cytologic Laboratory, University Hospital, Lund, Sweden. They were classified as follows: mild dysplasia, moderate dysplasia, severe dysplasia and CIS according to the definitions of the World Health Organization (321).

DEFINITIONS

With peroperative hemorrhage was meant blood loss in excess of 300 ml during the conization procedure. Postoperative hemorrhage implied blood loss originating from the cone cavity at any time from completion of the operation and until the cone cavity was healed and which required one or more of the following measures: suture, injection of adrenalin or vasopressin into the cone cavity, vaginal packing, application of M-cresosulphonic acid, infusion of tran-

examic acid and blood transfusion. Postoperative infection implied endometritis or salpingitis occurring within four weeks after conization. Stenosis implied cases of increasing dysmenorrhea associated with a narrow cervical canal after conization and cases with hematometra. The finding of a narrow cervical canal but without any symptoms did not allot a case to the group of cervical stenosis.

STATISTICAL METHODS

The following statistical methods were used: Fisher's exact test (II and III), Cochran's method for combining contingency tables (132) (II), Wilcoxon's rank sum test (III), chi-square test (IV and VI), analysis of

variance (IV), stepwise logistic regression analysis (117) (IV), life table technique (VI), Lee-Desu test (235) (VI), stepwise Cox's proportional hazard test (194) (VI) and product moment correlation (VI).

BLOOD LOSS ESTIMATION

For the determination of blood loss (III), all surgical towels and tampons used during the operative procedure, as well as all sanitary towels used during the first 24 hours after operation, were sampled. For blood loss determination a method based on the formation of alkaline hematin and described by Newton was used (294). The towels and tampons used during operation and the sanitary towels used during the first postoperative 24 hours were analysed separately. They were collected in a Cryovac^R plastic bag (14'' × 20'' × 200 g thickness) and 2 000 to 2 500 ml of 5% sodium hydroxide was added. The bag was placed in an automatic extractor (Stomacher Lab-Blender, model 3 500, Seward Laboratories, Suffolk, England) and processed until homogenisation was complete. At the

same time 100 ml of 5% sodium hydroxide was added to 1 ml of peripheral blood from the same individual for comparison. An aliquot of the homogenate was removed and filtered to clear the supernatant. After 30 minutes the optical density of the peripheral blood sample was analysed and immediately thereafter the optical density of the homogenate was analysed, both at 550 nanometer. The blood loss was calculated according to the formula:

$$\text{Blood loss (ml)} = \frac{\text{OD}_{550} \text{ of homogenate} \times v}{\text{OD}_{550} \text{ of peripheral venous blood} \times 100}$$

where v = volume of 5% sodium hydroxide added to the bag and OD_{550} = optical density at 550 nanometer.

RESULTS AND COMMENTS

COMPLICATIONS AFTER COLD KNIFE CONIZATION AND LASER CONIZATION

Mean and median peroperative bleeding for laser conization according to the technique described were 1.6 ml and 1.0 ml and range was 0–8.3 ml. For cold knife conization the corresponding figures were 16.3 ml, 8.4 ml and 0.8–98.0 ml. Bleeding during 24 hours after conization was mean 6.8 ml, median 3.3 ml and range 0–151.6 ml for laser conization and mean 80.0 ml, median 16.1 ml and range 1.8–1 565.1 ml for cold knife conization. Total amount of bleeding peroperatively and during the first 24 postoperative hours were 8.4 ml (mean), 4.6 ml (median) and 0.4–155.4 ml (range) for laser conization and 96.2 ml (mean), 30.1 ml (median) and 5.6–1 570.9 ml (range) for cold knife conization (III).

The differences were statistically significant ($p < 0.0001$; Wilcoxon's rank sum test) in favour of laser conization. Of special importance is the narrow range of bleeding in the laser group. There is no other prospective, randomized study in the literature comparing per- and postoperative bleeding at laser and cold knife conization. Dorsey & Diggs (108) in a non-randomized, non-comparing study reported 12 patients, where vasopressin and lateral sutures were used and they *estimated* the average peroperative blood loss to 1 ml. Berget reported on 30 patients in a similar way (35). Preliminary data from an ongoing prospective randomized study in Denmark concerning peroperative bleeding at laser conization and cold knife conization suggest less bleeding at laser conization (36) and are thus in accordance with our experiences.

Peroperative hemorrhage never occurred at laser conization and in 2 of 428 patients (0.5%) undergoing cold knife conization in study IV.

Postoperative hemorrhage is the most significant problem after cold knife conization. It occurred 173 times in 152 of 1013 (15.0%) women undergoing cold knife conization (I), in 8 of 55 (14.5%, equally distributed among early and late hemorrhages) cold knife conized women in the prospective, randomized study (III) and on 68 occasions in 61 of 428 (14.3%) cold conized patients in study IV and was thus practically constant during the 21-year period covered by these

studies. The reduction of the number of women with postoperative hemorrhages from 15.0% to 6%, which occurred during the last two years of study I is difficult to explain, but the reduction was not significant and only 25 of the 1013 conizations were performed during these two years.

For laser conization the number of women with postoperative hemorrhages was 1 of 55 (1.8%; III), 6 of 216 (2.8%; IV, laser conization on hospitalized patients) and 6 of 240 (2.5%; IV, laser conization as an out-patient procedure). The frequency of postoperative hemorrhages was significantly lower in laser conized patients ($p < 0.015$, III; $p < 0.00001$, IV). Furthermore, the postoperative hemorrhages were, with one exception, always more severe after cold knife conization than after laser conization. No laser conized patient experienced postoperative hemorrhage on more than one occasion. After cold knife conization the same patient could have postoperative hemorrhages up to four times.

Early hemorrhage (occurring within the first four days after operation) was the most common type of postoperative hemorrhage occurring after cold knife conization as well as after laser conization. After cold knife conization, postoperative hemorrhages occurred as late as the 31st postoperative day (I, III and IV). On the other hand no postoperative hemorrhages occurred after the 7th postoperative day after laser conization (III and IV).

Postoperative hemorrhage after cold knife conization generally occurs in 10–20% (4, 37, 41, 50, 55, 63, 89, 100, 107, 168, 190, 216, 297, 345, 357, 401) and our figures of 14–15% after cold knife conization are well within these limits. However, even figures of up to 40–50% have been reported (75, 415).

The bloodless technique of Scott (345) has reduced the peroperative bleeding, which is now seldom a problem at conization (IV) but has had no or little effect on the frequency of postoperative hemorrhages, which have remained at a high level. Different operative techniques have often been claimed to reduce the frequency of postoperative hemorrhages, but the few studies where different procedures have been used fail to verify this. Controlled studies are not available.

Laser conization according to the technique described herein gave a low and constant frequency of postoperative hemorrhages in a large number of patients operated upon over a period of time of more than two years (III and IV). Postoperative hemorrhages never occurred after the 7th postoperative day. We consider the combination of a vasoconstrictor substance and the CO₂ laser beam to be of utmost importance. With normal flow in the vessels, veins and arteries up to 0.5 mm in diameter are sealed by the laser. If the flow is stopped while the vessel is divided, those up to 2 mm are sealed (160). Vasopressin as a vasoconstrictor thus gives the temporary hemostasis during which the CO₂ laser beam can incise the tissue and seal the vessels, which is probably further accomplished by the vaporization of the cone cavity included in the technique. Without this temporary hemostasis troublesome bleeding may occur, which almost completely absorbs the laser energy.

Preliminary data from the earlier mentioned ongoing prospective, randomized study in Denmark gave 4% (2 of 47 patients) postoperative hemorrhage after laser conization and 19% (3 of 16 patients) after cold knife conization (36) and are thus in accordance with our results.

Dorsey & Diggs experienced no postoperative hemorrhages after laser conization in 18 patients (108).

Laser vaporization, *i.e.* destruction of the diseased cervical tissue or the whole transformation zone with the CO₂ laser instead of extirpating it, is also associated with a very low frequency of postoperative hemorrhages of 1.2 to 2.6% (30, 31).

After laser conization 109 hospitalized patients, who answered a questionnaire, experienced a slight to moderate spotting for mean 4.5 days (range 0–17 days), a slightly bloody discharge for 4.4 days (range 0–20 days) and a slight to moderate discharge for 8.3 days (range 0–23 days). After mean 17.3 days (range 2–29 days) effluence had stopped in all cases. 58 of the 109 women (53.2%) had no postoperative pain at all and the remainder experienced less pain than that associated with their normal menstruation, for a mean of 1.7 days (range 1–11 days) (IV).

The frequency of postoperative infections, as defined above, was for cold knife conization 1% (I) and 6.8% (IV). For laser conization it was 2.3% (hospitalized patients, IV) and 1.3% (out-patient procedure, IV). Laser conization was associated with significantly fewer postoperative infections than cold knife conization ($p = 0.0008$; IV). There were two cases of

salpingitis after cold knife conization. No tubal infections occurred after laser conization.

Infection after cold knife conization is reported to occur in about 1 to 25% of operations (33, 50, 75, 89, 107, 168, 190, 288, 345, 357, 391, 401) and the frequency after cold knife conization in our materials is thus well within these limits. Cold knife conization gives a considerable inflammatory reaction in the tissues, which can lead to increased morbidity at subsequent hysterectomy unless performed within 48 to 72 hours or postponed six weeks (403).

The reason for the significant reduction of postoperative infections after laser conization in comparison with cold knife conization might be the ability of the CO₂ laser beam to sterilize the tissue while excising the cone (160). We were, however, unable to completely eliminate postoperative infections and it might be speculated that these infections represented new infections not originating in the procedure (IV). However, the curettage performed after conization might also be of importance.

Stenosis after cold knife conization generally occurs in 1 to 30% of cases (37, 41, 75, 107, 168, 190, 219, 220, 222, 264, 334). The frequency of stenosis was 4.7% (20 of 428 patients) after cold knife conization, 0% after laser conization on hospitalized patients and 0.8% (2 of 240 patients) after laser conization as an out-patient procedure (IV). Laser conization thus had significantly fewer postoperative stenoses than cold knife conization ($p = 0.0002$). Also laser vaporization is reported to be associated with a very low frequency of stenosis (21, 22, 30, 31, 81, 407). The very low frequency of stenosis after laser treatment of the cervix seems to be inherent in the method and might be due to that healing occurs with very little fibroblastic proliferation (174, 285).

The total frequency of patients with at least one complication was 23.6% for cold knife conization, 5.1% for laser conization on hospitalized patients and 4.2% after laser conization as an out-patient procedure (IV). The complication rate has thus been significantly reduced by the new method described. To perform the laser conizations as an out-patient procedure did not increase the complication rate. On the contrary, these operations were associated with slightly less complications than laser conization on hospitalized patients.

It could be demonstrated (IV) that a conization performed during the menstrual period and during the post-partum period as well as a conization with free margins were associated with an increased risk of

postoperative hemorrhage ($RR = 1.45$; $p = 0.046$ for conization performed during menstruation and post-partum. $RR = 1.50$; $p = 0.007$ for conization with free margins). Conizations performed in the menopause were associated with an increased risk of stenosis ($RR = 1.60$; $p = 0.025$). Significantly more laser conizations were performed during menstruation and in the post-partum period ($p = 0.0073$) and significantly more laser cones had free margins ($p = 0.0003$). At cold knife conization 10–80 ml vasopressin was used. At laser conization 5–40 ml was used. Extra sutures for hemostatic purpose were used in 41.4% (cold knife conization), 2.8% (laser conization, hospitalized patients) and 4.6% (laser conization as an out-patient procedure). These differences are statistically significant in favour of laser conization ($p < 0.00001$ for both parameters).

Laser conization thus had significantly fewer post-operative complications, despite the fact that these operations were associated with significantly more factors prone to increase the rate of postoperative complications (conization performed during menstruation and in the post-partum period as well as conization with free margins). There was no tendency towards changes in complication rates within groups with time.

LATE SEQUELAE AFTER COLD KNIFE CONIZATION

The effect of cold knife conization on subsequent pregnancy was analysed (II). In women 21–25 years old there was a significant increase in the risk of premature delivery AC compared with that BC, both for those pregnant BC ($p < 0.02$) and those not ($p < 0.001$). The rate of premature deliveries in this age group was 4.4% BC and 30.6% AC. Nulliparous women ≥ 31 years had significantly more premature deliveries AC than parous ones ($p < 0.03$).

The frequency of late spontaneous abortions was not significantly increased in any age group.

Length of labor AC was notably short in non-parous women (4.5–9 hours) and in parous women term delivery started with rupture of the membranes significantly more often than BC ($p < 0.001$). Cervical stenosis, defined as the need to perform cesarean section, cervical incision or cervical dilatation because of a rigid cervix, which failed to dilate in spite of good labor, occurred in none of 268 term deliveries BC and

in 9 of 164 term deliveries AC. This difference was statistically significant ($p < 0.002$). However, the stenosis was of clinical importance in only one case, where it was necessary to perform a cesarean section.

There was no over-representation of early postoperative complications after conization in cases with premature deliveries, spontaneous abortions or cervical stenosis AC. The total perinatal mortality rate during the study period was 2.0%, compared with 2.1% BC and 3.0% AC in the conized women.

108 women during the years 1970 to 1976 had a cervical cerclage applied in gestational week 13–14 in pregnancies after conization. Prophylactic cerclage did not reduce the incidence of either premature deliveries or late spontaneous abortions. No significant differences could be found in socio-economic status, smoking habits, medical disease, gynecologic disease and gynecologic operations between women BC and AC. Nor could any such differences be demonstrated AC for women pregnant BC and women not pregnant BC. Within groups with and without prophylactic cerclage at pregnancy AC there were no differences in these factors BC and AC.

The cones were not actually measured, but 94% of cones containing CIS and 98% of cones harbouring dysplasia had free margins of resection. The top of the cone was adjusted to be just distal to the internal os and not engaging it. The cones could thus be regarded as large ones. Leiman has shown that the risk of premature deliveries and of late spontaneous abortions increases with increasing size of the cone (237). Increased risk of premature deliveries after conization in young and nulliparous women is probably the maximum side effect of conization on subsequent pregnancy.

Also Bjerre found a greater risk of premature delivery AC in non-parous women, who had 16% premature deliveries compared with 8% premature deliveries in parous women (42).

The negative consequences of conization can probably be reduced if the cone size is individualized with the aid of colposcopy. Young women mostly have only exocervical changes, which make more shallow cones justifiable with no hazards regarding the histo-pathologic interpretation.

The literature on the outcome of pregnancy after conization is contradictory. Most reports conclude that conization does not constitute a hazard to the outcome of future pregnancies (24, 60, 82, 98, 155, 225, 226, 228, 239, 248, 257, 264, 270, 317, 374, 377, 396).

However, since Miller's & Todd's report (276) that conization can lead to impaired outcome of pregnancy, other authors have come to the same conclusion (128, 151, 154, 158, 176, 189, 196, 202, 210, 236, 254, 277, 315).

These contradictory conclusions can probably to a great extent be explained by different techniques used at conization, the cone size and possibly also by the rate of early complications after conization in different materials. The way in which the materials are analysed is also of importance. Most older materials only report on the outcome of pregnancy AC and make no comparison with the outcome BC or with control groups. Two recent reports used the statistical method with matched controls and reached completely contradictory results regarding the risk of premature delivery AC (189, 396). If a group of women submitted to conization also constitutes an obstetrical risk population BC is not revealed by this method (41).

Analysing comparable age groups within a sufficiently large material before and after conization, considering apart from age, increasing parity, socioeconomic status, smoking habits, surgical interventions, various diseases and possible other influencing factors is probably the best model. Buller & Jones, using in part this type of analysis, found no negative effects of conization on subsequent pregnancies (60).

Some authors recommend prophylactic cerclage in pregnancies following conization (196, 236, 237). We were unable to demonstrate that this procedure reduced the risk of premature deliveries or late spontaneous abortions.

LONG TERM FOLLOW-UP AFTER COLD KNIFE CONIZATION

1 013 women were followed cytologically and clinically after cold knife conization (I). The indications for conization were group V smears in 600 cases, group IV smears in 315 cases, group III smears in 64 cases and group II smears in 34 cases. Histo-pathological investigation of the cone specimens revealed invasive carcinoma in 19 instances (1.9%) and microinvasive carcinoma in 7 instances (0.7%). Invasive and microinvasive carcinoma were found even in patients with the lowest degree of cytological abnormality. There was one case of invasive carcinoma (1.6%) among 64 patients with group III smears and one case each of invasive and microinvasive carcinoma (5.8%) among 34 patients with group II smears. There were 718

cases (70.9%) of CIS and 169 cases (16.7%) of various degrees of dysplasia (40 times mild, 92 times moderate and 37 times severe). In 100 instances (9.8%) the cone was considered benign. In 9 of these 100 cases conization was preceded by four quadrant biopsies and electrocoagulation, which thus apparently completely eradicated the pathologic epithelium and in only 91 of 1 013 cone specimens (9.0%) no pathologic changes were found, which could explain the abnormal vaginal smear. Further sectioning of these cones would probably have lowered this figure. Furthermore, in this group of 100 women, seven again developed pathologic smears and secondary treatment in the form of reconization and/or hysterectomy revealed one case of mild dysplasia and two cases of CIS.

166 of 169 cones (98.2%) containing dysplasia had free resection margins. For CIS this figure was 672 of 718 (93.6%).

Primary conization cured 156 of 159 (98.1%) women with dysplasia after exclusion of those hysterectomized for other conditions or lost to follow-up. All 37 patients with severe dysplasia had negative smears at follow-up.

620 of 689 patients (90.0%) with CIS not hysterectomized for other gynecological conditions or lost to follow-up had negative smears during the observation period. This figure depended on whether the resection margins of the cone were free from pathologic epithelium or not. If they were free 597 of 647 patients (92.3%) had negative cytology at follow-up. If the resection margins were doubtfully free cytology returned to normal in 23 of 36 patients (63.9%) after conization. All the six patients with marginal growth had pathologic smear at follow-up and were subjected to secondary treatment.

The three patients, who again developed pathologic smear after conization for dysplasia, were detected at first control after three months. Pathologic smears occurring after conization for CIS with doubtful or not free margins all developed within the first year after conization. 33 of 50 pathologic smears after conization for CIS with free margins developed within the first year and represent thus by definition persistent disease. If smears were negative the first year after conization for CIS with free margins of resection, the risk of again developing severe dysplasia or CIS was 2.3% and the yearly incidence during the next four years was 0.7%.

In one patient with a pathologic smear at the first follow-up visit after conization for CIS with not free

margins, reoperation revealed a microinvasive carcinoma, which most certainly was present at the time of first conization. No patient developed invasive or early invasive carcinoma during the follow-up period. All patients were followed for at least one year and after that time only 3.6% of patients with dysplasia and 1.4% of patients with CIS were lost to follow-up.

Primary conization thus cured 90% of patients with carcinoma in situ. If also reconizations are considered, this figure rose to 94%. The excellent results with conization as therapy have been repeatedly documented (4, 13, 14, 20, 38, 40, 41, 44, 51, 53, 61, 65, 73, 74, 76, 77, 91, 92, 93, 118, 122, 127, 130, 134, 141, 143, 145, 147, 149, 150, 152, 154, 167, 169, 171, 172, 177, 178, 179, 180, 190, 196, 198, 200, 201, 204, 207, 209, 211, 213, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 228, 242, 248, 256, 265, 267, 268, 269, 272, 280, 281, 286, 292, 297, 299, 300, 301, 303, 327, 329, 342, 347, 355, 357, 362, 364, 379, 384, 385, 386, 404, 413, 415). It is surprising that hysterectomy still is standard treatment for CIS in many parts of the world (for references, see introduction). Follow-up is necessary after both types of treatment. Invasive carcinoma may develop after conization as well as after hysterectomy (41, 213).

The old rule at follow-up was to take a vaginal smear at least once a year for ever. On the other hand, Burghardt & Holzer (68) showed that the risk of recurrence was related to the reliability of the primary diagnosis. Among 634 cases treated with conization, where the cones were extensively sectioned and found to have free margins, they found no invasive recurrences and only 0.3% preinvasive recurrences (mild dysplasia) after 5 to 21 years of follow-up. Wolf found 0.5% recurrences after conization with free margins when studying 3129 cases reported by 57 different authors (404). Bjerre (41) and Kirkup & Singer (205) found after exclusion of cases representing persistent disease the frequency of recurrences after conization with free margins to be the same as the incidence for carcinoma in situ in the general population. This might indicate that after two or three negative smears, for exclusion of persistent disease during the first postoperative year, the patient can be included in ongoing mass screening programs.

Also in the present material (I) most pathologic smears developed within the first year and represent persistent disease. Unfortunately, we experienced a higher recurrence rate than the incidence for CIS, similar to the findings from British Columbia (53). A possible explanation for this is that a certain propor-

tion of cones containing CIS indeed did not have free margins and that this was not revealed on routine pathological examination. Most of the patients developed pathological smears within the first year of observation, a fact that agrees with this point of view.

1.9% of the cones contained occult invasive carcinoma. This is within the 2 to 7% usually reported in other large conization materials (4, 41, 53). However, figures of over 20% have been reported (145). In these cases the cone margins accidentally often go through frank invasive carcinoma. There is probably an increased risk of spreading malignant cells into the general circulation during such a procedure (50, 182).

The occurrence of invasive carcinoma also in smears belonging to groups II and III is a strong argument for histo-pathologic clarification of all pathologic smears, also those of lesser severity (27, 153).

SHORT TERM CYTOLOGIC AND COLPOSCOPIC FOLLOW-UP AFTER LASER CONIZATION

333 women were followed with cytology and colposcopy for 4 to 24 months after laser conization (V). Five conization specimens (1.5%) contained occult invasive carcinoma, 34 (10.2%) early invasive carcinoma, 203 (61.0%) severe dysplasia or CIS, 59 (17.7%) moderate dysplasia and 32 (9.6%) contained mild dysplasia. Free margins of resection were noted in 88.2% (30/34) cones with early invasive carcinoma, in 91.1% (185/203) of cones with CIS or severe dysplasia, in 94.9% (56/59) cones with moderate dysplasia and in all cones with mild dysplasia (32/32). The number of cones with resection margins free from atypic cells is greater than is usually reported after cold knife conization. This might be due to that the tissue damage along the resection margins caused by the CO₂ laser was minimal, seemingly less than after cold knife conization, which might facilitate the histo-pathologic evaluation.

The five patients with occult stage IB invasive carcinoma as well as two patients with early invasive carcinoma with free resection margins but with CL-invasion underwent radical Wertheim hysterectomy and bilateral pelvic lymphadenectomy. The four patients with early invasive carcinoma and with resection margins not free from atypic epithelium underwent an extended hysterectomy.

In 322 patients laser conization was thus the only treatment. 308 of these (95.7%) had normal cytology

and colposcopy at follow-up. For early invasive carcinoma (all with free margins of resection) this figure was 96.4%, for CIS or severe dysplasia it was 97.8% (free margins of resection) and 83.3% (margins not free). For moderate dysplasia it was 94.6% (free margins) and 100% (margins not free). Cases of mild dysplasia (all with free margins of resection) had normal cytology and colposcopy in 90.6% at follow-up.

In 14 patients cytology and colposcopy did not revert to normal after one laser conization. In 13 of these 14 cases abnormal cytology or colposcopy was present already at the first check-up and they thus represent persistent disease. One patient with CIS and non-free cone margins had normal cytology and colposcopy at 6 and 12 months, but had a pathologic smear at 18 months.

In 137 of 159 women (86.2%) personally investigated (HG & GL) the transformation zone was completely visible after laser conization and in 22 (13.8%) it was not fully visible. In no case was the transformation zone completely hidden in the endocervical canal. Also for laser vaporization the transformation zone is reported to be fully visible in a high proportion of cases (30). After cryosurgery it is often relocated high up in the endocervical canal (21). The colposcopic picture was almost pathognomonic, with the hair needle capillaries fanning radially from the periphery towards the os. Healing occurred within 4 to 6 weeks in these cases.

The period of follow-up was short, due to the fact that the technique of laser conization is relatively new. 224 of the 308 patients (72.7%), where one laser conization was the only treatment, were followed for one year or more. There is, however, no reason to believe that the results of long term follow-up should be inferior to those achieved after cold knife conization. On the contrary, the vaporization of the cone cavity after excision of the cone included in the technique might increase the "cure rate" in cases with doubtful or not free margins as compared with the "cure rates" after cold knife conization in such cases.

We thus experienced only 4.3% treatment failures after one laser conization during the observation period, despite the fact that also cases with early invasive carcinoma were included. The frequency of treatment failures for CIS or severe dysplasia was 3.4%; for moderate dysplasia it was 5.1% and for mild dysplasia 9.4%. For all preinvasive changes together treatment failures occurred in 4.4%. Also a considerable proportion of cases of CIS or severe dysplasia (83.3%, or 15 of 18 cases) with resection margins not

free from atypic cells had normal colposcopy and cytology at follow-up.

For laser vaporization is reported 7 to 37% treatment failures for all types of preinvasive changes at short term follow-up (21, 22, 30, 31, 70, 81, 166, 262). For severe dysplasia and carcinoma in situ laser vaporization fails in 13 to 32% after one treatment (21, 22, 30, 31, 70, 81). Best results with laser vaporization are achieved if the amount of tissue vaporized equals that of a normal sized cone (407).

We did not use tissue destructive methods (cryosurgery, electrocoagulation or laser vaporization) in the treatment of preinvasive cervical changes. A guiding principle in the treatment series presented (I and V) has been always to extirpate the whole lesion together with the transformation zone, thereby making a careful histo-pathologic evaluation possible. Furthermore, tissue destructive methods can be used only in selected cases, where the whole transformation zone and lesion are colposcopically visible.

In the series presented (V) we noted less treatment failures among patients with the most severe intraepithelial changes and most failures occurred among patients with mild dysplasia. This finding is difficult to explain and is the opposite to what is usually reported.

The series contained 1.5% occult invasive carcinoma. The carbon dioxide laser has been shown to seal lymphatics and blood vessels (160). This might be of importance in reducing the risk of spreading malignant cells into the circulation when inadvertently cutting in frankly malignant tissue (182).

ON THE ROLE OF CONIZATION IN EARLY INVASIVE CARCINOMA OF THE UTERINE CERVIX

A clinical, histo-pathological and statistical analysis was undertaken in cases of early invasive carcinoma of the uterine cervix (VI). The observation period was 2 to 20 years. During this period 21 of 262 women (8.0%) developed invasive or early invasive recurrences. 16 of 17 invasive recurrences were local (central and/or lateral). Invasive recurrences occurred after 1 to 17 years (mean 6.4 years, median 6.0 years). The corresponding figures for early invasive recurrences were 2 to 12 years, 6.8 and 6.5 years. The figures represent minimum figures because more patients will develop recurrences.

All recurrences were verified by histo-pathological

investigation of tumor tissue or by investigation of fine needle aspirates. 11 of the 262 women (4.2%) died of recurrent invasive cervical carcinoma.

164 patients (62.1%) had no symptoms at the time of diagnosis. Postcoital bleeding or bleeding after physical effort occurred in only 17 patients (6.4%). Gynecological examination at the time of diagnosis revealed an epithelialized portio in 52.3% of women and an ectopia with no clinical suspicion of malignancy in 47.7% of the patients.

Vaginal smears were positive or aroused suspicion of malignancy in 90.9%. 24 women (9.1%) had no vaginal smear taken and the diagnosis was primarily suspected at dilatation and curettage. Colposcopy was only rarely used.

Mean tumor depth was 2.3 mm and range was 0.2 to 9.0 mm when diagnosis was based on cone, uterus or both. When the diagnosis was based on wedge biopsies these values were 1.4 mm and 0.4 to 4.6 mm. The infiltration was significantly less deep when diagnosis was based on wedge biopsies ($p < 0.0001$). Lateral extension of tumors was 4.6 mm (range 0.4–17.2 mm).

Invasive buds were the most common type of infiltration, occurring in 45.8% (diagnosis on cone, uterus or both) and 49.4% (diagnosis on wedge biopsies) of cases. Most tumors were moderately differentiated and were of the large-cell non-keratinizing type.

There were no significant differences in type of infiltration, degree of differentiation or cell type between tumors where the diagnosis was based on conization, uterus or both and tumors where diagnosis was based on wedge biopsy. However, the frequency of evident and suspected CL-invasion was significantly lower in tumors, where the diagnosis was based solely on wedge biopsies ($p < 0.02$). CL-invasion occurred in 9.5% of cases where the diagnosis was based on cone, uterus or both and in 5.1% where it was based on wedge biopsy. Corresponding figures for strong suspicion of CL-invasion were 18.9% and 7.6%.

Factors of prognostic importance were searched for using the life table technique and the Lee-Desu test as well as stepwise Cox's proportional hazard test. The life table technique revealed the following risk factors: an epithelialized portio at the time of diagnosis ($p = 0.012$), CL-invasion or strong suspicion of such ($p = 0.002$) and doubtfully free resection margins on a diagnostic cone ($p = 0.026$).

The 15-year survival rate for women, whose portio was epithelialized at the time of diagnosis, was only

89.5% versus 99.1% if an ectopia was present. Corresponding figures for CL-invasion, strong suspicion of CL-invasion and absence of CL-invasion were 82.0%, 87.8% and 97.2% respectively. The 15-year survival rate for women with doubtfully free margins on a diagnostic cone was 83.3% compared with 96.8% for the rest of the patients.

The Cox's analysis revealed, apart from the above mentioned risk factors, also that treatment with conization or simple hysterectomy constituted an additional risk factor, especially in the presence of the above mentioned factors. An epithelialized portio at the time of diagnosis increased the risk of death of recurrent invasive cervical carcinoma 11.3 times, CL-invasion or strong suspicion of such increased this risk 5.2 times, doubtfully free margins on a diagnostic cone increased it 5.3 times and finally treatment with conization or simple hysterectomy increased the risk for death from recurrent invasive cervical carcinoma 3.7 times. The effect of the different risk factors was multiplicative.

Depth of tumor, as measured from the basement membrane, was of no prognostic importance. Nor was lateral extension of tumor. Confluent growth did not constitute a risk factor in this material. Tumors of the large cell keratinizing type were a prognostically favourable sign ($p = 0.023$).

It could be demonstrated that biopsies were not adequate diagnostic material because of a significantly lower detection rate of CL-invasion or strong suspicion of such ($p < 0.02$). The cone biopsy, however, provides adequate information about prognostic factors in cases of early invasive carcinoma of the uterine cervix.

An epithelialized portio at the time of diagnosis has not earlier been reported as a risk factor. It is not mediated through co-variation with other known factors which were tested. The significance was so strong, that it most certainly cannot represent an artefact. It might be that these endocervically located tumors are more often multifocal and discontinuous, and that, even in cases with free cone margins, more tumor foci were left behind.

Tumor invasion in CL-spaces is agreed upon by most authors as a risk factor (17, 45, 54, 185, 253, 346). Others deny that it is of any prognostic importance (238, 322). In the present material also strong suspicion of CL-invasion was a prognostically unfavourable sign. Unclear conization margins as a risk factor is also recently described by others (346).

The histologic type and degree of differentiation

have seldom been systematically determined in these early cancers (32). We could demonstrate that large cell keratinizing tumors were associated with a good prognosis. In comparison, the degree of differentiation was not found to be of prognostic importance. This could be due to the present material being too small for a definite settling of this matter.

For more advanced invasive carcinomas of the uterine cervix both degree of differentiation and cell type have been frequently studied and considered to be of prognostic importance (57, 261, 397, 398). Recently, Stendahl has constructed a malignancy grading system and applied it to invasive carcinomas stage IB–IV (358). He found a good correlation between this system and the outcome of the patients. His parameters were: structure of tumor, differentiation into cell type, nuclear polymorphism, number of mitoses, mode of invasion, stage of invasion, lympho-vascular invasion and lympho-plasmocytic response, where the four first mentioned concern the tumor cell population and the rest reflect the tumor-host relationship. Of these, structure of tumor and stage of invasion are only applicable to more advanced cancers and were not studied by us. Opposite to our findings and those of Wentz (398) Stendahl found differentiation into cell type as a single factor to be of no prognostic importance. We did not systematically study the lympho-plasmocytic response, but our impression is that it was marked or at least moderate in all these early cases.

Of 56 patients with absence of risk factors (epithelialized portio, evident or suspected CL-invasion, doubtful margins on a diagnostic cone), 25 were treated with conization and 31 with simple hysterectomy. Maximum tumor depth was 4.0 mm and maximum lateral extension of tumor was 8.0 mm. No patient died from recurrent invasive cervical carcinoma and only one, in the hysterectomy group, developed a recurrence.

In the presence of risk factors early invasive carcinoma of the uterine cervix should be treated as frank invasive carcinoma. In the absence of risk factors conization with free margins of resection or simple hysterectomy seem to be sufficient treatment and the latter has probably no advantages over the former.

TECHNICAL ASPECTS ON LASER CONIZATION

Before us Toaff (372) attempted conization with the laser scalpel. He experienced abundant bleeding,

difficulties in obtaining the proper cutting angles and found the technique cumbersome in the narrow confines of the vagina and therefore soon abandoned it. Laser excisional biopsy was replaced by laser vaporization of preinvasive disease of the cervix (2, 28, 29, 81). The primary treatment failures were high with this method, but were reduced after Anderson's investigations concerning the treatment depth necessary to eradicate the preinvasive epithelium engaging cervical crypts (9).

It was not until 1979 that excisional laser surgery on the cervix was again introduced. This year Dorsey & Diggs (108) reported on 30 patients undergoing microsurgical conization of the cervix. The laser was mounted on an operative microscope with 300 mm focal distance of the lens. This gave a spot size of 1.5 mm and a substance loss of 1.6 mm (50–100 micrometer of thermal necrosis on each side of the beam according to Hall (160) and unrelated to power output and time exposure). Using a 400 mm focusing lens results in 2.0 mm spot size and thus 2.1 mm of substance loss. This is a considerable substance loss, which can, for example, completely eradicate a focus of CL-invasion, a factor of great prognostic importance in cases of early invasive carcinomas (VI).

We used the laser beam not coupled to an operation microscope. The focal length of the lens was 125 mm and the spot size was 0.22 mm. The combined width of tissue vaporized and destroyed was only 0.32 mm. This substance loss is 5 to 6.6 times less than if the laser beam is coupled to an operative microscope. Performing colposcopy before conization does not reduce the frequency of cones with free margins. On the contrary, we had a high percentage of cones with free margins, over 90% (IV).

Beneath the thermal necrosis there is an area of various degrees of thermal cellular damage. The depth of this area is directly related to the exposure time of the laser beam on the tissue and is usually about 500 micrometer. The small spot size used by us resulted in high power densities, making fast cutting possible, thereby reducing exposure time and minimizing this area of partial cellular damage.

All histologic sections of the laser cones were of good quality. The margins were covered by a rather thin layer, approximately 30 to 40 micrometers, of carbonized tissue and a rather narrow zone, approximately 200 to 400 micrometers, of various degrees of thermal damage. No difficulty occurred in judging whether the resection margins were free, or not free, from cells with atypias (III). The substance loss was

as a rule less than that experienced after cold knife conization (6).

CLINICAL IMPACT OF LASER CONIZATION

It has been repeatedly demonstrated (in this thesis and in the survey of the literature made therein) that the minor surgical procedure of cold knife conization is linked with an unproportionately high frequency of major complications. This thesis has shown laser conization to be a both simple and safe procedure. It is evident from our investigations that laser conization can be performed on an out-patient basis. The minor surgical procedure of conization is now, with the method described herein, associated with a minor rate of early complications.

This highlights the present controversy between those who use tissue destructive methods (electrocoagulation, cryosurgery, laser vaporization) and those who claim that an excisional cone biopsy is always necessary for adequate histo-pathological clarification and of importance for the final outcome of the patient.

This new method promises to give optimal histo-pathologic confirmation of the diagnosis, and is as-

sociated with as few early postoperative complications as the above mentioned tissue destructive methods. Follow-up is associated with few problems, as the junction remains colposcopically visible in a high proportion of cases.

Furthermore, it is evident that great savings of hospital costs are obtained and that patient discomfort is reduced. Only in our hospital, the estimated cost reduction amounts to roughly one million Swedish crowns per year. Knowing the nature of the whole lesion and having information about the resection margins forms a better basis than a small biopsy sample for the decision regarding check-up intervals, which need reasonably be made less frequently than after tissue destructive methods, thereby further reducing the costs.

It is yet too early to say anything regarding late sequelae after laser conization, *i.e.* possible negative consequences on the outcome of further pregnancies. It is, however, very likely that the increased precision inherent in this procedure with its minimal bleeding, its minimal tissue damage and the special healing characteristics of the laser lesion (174, 285) might mean that laser conization also in this respect is superior to cold knife conization. This, however, awaits further evaluation.

CONCLUSIONS

1. Cold knife conization was associated with a major rate of complications in a large material covering a period of 21 years. The complication rate was inherent in the method and did not change with time.
2. Cold knife conization had some negative effects on the outcome of future pregnancies in certain age groups.
3. Cold knife conization was effective treatment in the vast majority of patients with pre-invasive cervical carcinoma and primary conization cured 90% of patients. If also reconizations are considered this figure rose to 94%.
4. Most pathological smears developed within the first year after conization.
5. Laser conization significantly reduced the frequency of early complications. The procedure could be performed on an out-patient basis without increasing the risk of postoperative complications, thereby considerably reducing hospital costs.
6. Laser conization gave good "cure rates" in a short term follow-up study after treatment for preinvasive and early invasive cervical carcinoma. On methodological grounds it can be assumed that results of long term follow-up will be as good as or probably better than after cold knife conization.
7. Conization has a role in the treatment of early invasive carcinoma of the uterine cervix in the absence of prognostically unfavourable factors (epithelialized portio at the time of diagnosis, suspected or evident CL-invasion, doubtful margins on a diagnostic cone).

As evident from the above, laser conization is a method, which not least for economical reasons, probably will replace cold knife conization in the future.

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